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Ethanol Abolishes Ischemic Preconditioning in Humans

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Objectives This study sought to assess the effect of acute alcohol intake on ischemic preconditioning (IPC) in humans using the clinical model of 2 sequential balloon inflations during a percutaneous coronary intervention (PCI).

Background Ischemic preconditioning is the most potent form of endogenous myocardial protection from irreversible ischemic injury. Experimental observations suggest that acute ethanol administration might abolish IPC.

Methods We studied 30 consecutive patients (22 men, mean age 65 years) undergoing elective coronary angioplasty who were randomized to receive an oral dose of 40 g ethylic alcohol (administered as 149 ml of Gordon's Gin) or 149 ml of water 30 min before PCI. Intracoronary electrocardiogram was continuously monitored to assess the greatest ST-segment elevation or depression from baseline.

Results In placebo-treated patients, the change of ST-segment shift during the second inflation was significantly smaller than that during the first inflation (19.3 ± 9.1 vs. 15.7 ± 8.7, $p = 0.005$). In contrast, in gin-treated patients, the change of ST-segment shift during the second inflation was significantly greater than that during the first inflation (18.7 ± 7.2 vs. 22 ± 10, $p = 0.03$). The group–inflation interaction for ST-segment changes was highly significant ($p < 0.001$).

Conclusions This randomized, prospective study in humans shows that administration of a moderate dose of ethanol abolishes IPC occurring during sequential episodes of myocardial ischemia and is associated with worsening ischemia. Based on our study, intake of moderate to high doses of alcoholic beverages should be avoided in patients at high risk of acute myocardial infarction. (J Am Coll Cardiol 2008;51:271–5) © 2008 by the American College of Cardiology Foundation

Ischemic preconditioning (IPC) is the most potent form of endogenous myocardial protection from irreversible ischemic injury. The first demonstration of IPC was obtained in a canine model of myocardial infarction by Murry et al. (1), who showed that infarct size was reduced from 29% to 7% when prolonged coronary ligation was preceded by short cycles of ischemia-reperfusion. Ischemic preconditioning has been shown in several animal species and seems to occur also in humans (2).

Moderate alcohol consumption is associated with a lower risk of cardiovascular events, probably mediated by beneficial effects on inflammation (3), lipids, and coagulation (4). In contrast, binge and/or heavy drinking with alcohol intake >50 g per session is associated with higher cardiovascular risk and mortality after acute myocardial infarction (5,6). Interestingly, recent experimental observations indicate that acute ethanol administration might abolish IPC (7).

Thus, in this study we assessed the effects on IPC of acute exposure to ethanol in humans using the surrogate model set up in previous clinical studies (8), based on the assessment of myocardial ischemia during sequential balloon inflations in the setting of a percutaneous coronary intervention (PCI).

Methods

Patients. We studied 30 consecutive patients (22 men; mean age 65 years, range 51 to 76 years) who underwent successful PCI for an isolated obstructive stenosis (internal diameter reduction of 70% to 90% at visual analysis) in the proximal two-thirds of a major epicardial coronary artery. Inclusion and exclusion criteria have been previously described (8). All patients gave written informed consent for participation in the study, which was approved by our institutional ethics committee.

Study protocol. In this prospective, randomized, open-label, blinded examination study, which was performed within 5 days of diagnostic coronary angiography, we

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Abbreviations and Acronyms

ECG = electrocardiogram
IC = intracoronary
IPC = ischemic preconditioning
PCI = percutaneous coronary intervention

allocated 30 consecutive patients to 2 groups. One group consisted of 15 patients who received an oral dose of 40 g ethanol (administered as 149 ml of Gordon's Gin) 30 min before PCI. The other group consisted of 15 patients who received 149 ml water 30 min before PCI. The time of 30 min was chosen to achieve peak blood levels of ethanol. All patients were on oral aspirin (100 mg), clopidogrel (75 mg), and statins. No anti-ischemic treatment was given in the last 24 h before PCI. No patient received sublingual or intravenous nitrates in the last 24 h before the study or throughout the study. Patients were not premedicated with diazepam or other sedatives.

The PCI protocol for IPC assessment was previously described in detail (8). Briefly, 2 sequential 2-min balloon inflations separated by a 5-min interval were performed. The entity of ST-segment shift (in millimeters) was measured by intracoronary (IC) electrocardiogram (ECG) as an index of myocardial ischemia during balloon occlusion. Furthermore, patients were asked to score the intensity of cardiac pain during ischemia by a visual analog scale ranging from 0 to 100.

Determination of blood ethanol levels. In the last 5 gin-treated patients, venous blood samples were obtained for the measurement of ethanol levels using the DRI ethyl alcohol assay (Microgenics, Freemont, California) at baseline and 30 min after gin administration, immediately before the study protocol.

Statistical analysis. Comparisons between groups of continuous and categorical variables were performed using an unpaired Student *t* test and chi-square test, respectively. Intragroup comparisons were performed using a paired Student *t* test. Two-way analysis of variance for repeated measures was used to compare ischemic ECG changes and pain intensity during balloon inflations in the 2 groups of patients. Bonferroni correction as a post-hoc test was applied for multiple comparisons in case of global statistical significance after a 2-tailed Student *t* test. Correlations were performed using a Pearson test. Data are expressed as mean ± standard deviation if not otherwise specified; $p < 0.05$ was considered significant. Assuming a difference of 6 mm in the changes of ST-segment shift from the first to the second balloon inflation between the 2 groups, we calculated that 15 patients per group were required to have an 80% power to detect a statistically significant difference between groups at $p < 0.05$.

Table 1 Clinical and Angiographic Features in the 2 Groups of Patients

	Gin (n = 15)	Placebo (n = 15)	p Value
Age (yrs)	62.3 ± 9.3	67.8 ± 8.5	0.1
Gender male, n (%)	11 (73.3)	11 (73.3)	1
Diagnosis, n (%)			1
Stable angina	6 (40)	7 (47)	
Unstable angina	9 (60)	8 (53)	
Hypertension, n (%)	11 (73.3)	13 (86.7)	0.65
Smoking, n (%)	7 (46.7)	6 (40)	1
Diabetes, n (%)	3 (20)	8 (53.3)	0.12
Family history of IHD, n (%)	7 (46.7)	8 (53.3)	1
Dyslipidemia, n (%)	7 (46.7)	10 (66.7)	0.46
Culprit vessel, n (%)			0.65
LAD	5 (33.3)	5 (33.3)	
LCx	5 (33.3)	7 (46.7)	
RCA	5 (33.3)	3 (20)	
Reference diameter (mm)	2.95 ± 0.51	2.88 ± 0.55	0.73
Severity of stenosis (%)	83 ± 7	85 ± 5	0.37

IHD = ischemic heart disease; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

Table 2 Hemodynamic Features in the 2 Groups of Patients

	Gin (n = 15)	Placebo (n = 15)	p Value
Systolic arterial pressure (mm Hg)			
Baseline	124 ± 23	132 ± 20	0.31
First inflation	117 ± 33	126 ± 16	0.35
Second inflation	129 ± 16	125 ± 16	0.5
Diastolic arterial pressure (mm Hg)			
Baseline	77 ± 10	78 ± 13	0.7
First inflation	85 ± 8	84 ± 11	0.66
Second inflation	90 ± 12	84 ± 11	0.13
Heart rate (beats/min)			
Baseline	72 ± 10	75 ± 14	0.5
First inflation	73 ± 10	78 ± 12	0.22
Second inflation	73 ± 14	74 ± 14	0.82

Values are measured at the highest ST-segment shift at intracoronary electrocardiogram during the first and the second inflation. Data are expressed as mean ± SD.

Results

Clinical, angiographic, and hemodynamic features. Clinical and angiographic features were similar in the 2 groups (Table 1). Hemodynamic variables during PCI were also similar in the 2 groups and in each group during the first and the second balloon inflation (Table 2). The mean time from alcohol administration to the first balloon inflation was 31 min (range 28 to 33 min).

Myocardial ischemia. The ST-segment before the first and the second balloon inflation was at the isoelectric line both in placebo and gin-treated patients. Table 3 summarizes values of ST-segment shifts and times to 1-mm ST-segment shift on IC-ECG during balloon inflation in the 2 groups, as well as times to normalization of ST-segment shift after balloon deflations.

In placebo-treated patients, the change of ST-segment shift during the second inflation was significantly smaller than that during the first inflation (19.3 ± 9.1 mm vs. 15.7 ± 8.7 mm, $p = 0.005$). In contrast, in gin-treated patients, the change of ST-segment shift during the second inflation was significantly greater than that during the first inflation (18.7 ± 7.2 mm vs. 22 ± 10 mm, $p = 0.03$) ($p <$

Table 3 Values of ST-Segment Shift, Time of Onset of ST-Segment Shift ≥1 mm, Time to ST-Segment Shift Normalization, and Cardiac Pain Severity

	Gin (n = 15)	Placebo (n = 15)	p Value
ST-segment shift from baseline to ST-segment maximum on IC-ECG (mm)*			
Inflation 1	18.7 ± 7.2	19.3 ± 9.1	0.83
Inflation 2	22 ± 10†	15.7 ± 8.7‡	0.07
Time to 1-mm ST-segment shift (s)§			
Inflation 1	20.1 ± 7.8	24.4 ± 12.8	0.28
Inflation 2	20.8 ± 10.1	31 ± 15.1†	0.04
Time to ST-segment shift normalization (s)			
Inflation 1	22.1 ± 5.5	22.9 ± 3.9	0.65
Inflation 2	22.3 ± 4.7	23.1 ± 3.5	0.60
Pain severity (mm)			
Inflation 1	68.4 ± 27	71.2 ± 27	0.78
Inflation 2	61.4 ± 30.5	57.8 ± 23.6‡	0.72

Data are expressed as mean ± SD. *Group–inflation interaction is statistically significant ($p < 0.0001$). †$p < 0.05$ versus first inflation value. ‡$p = 0.01$ versus first inflation value. §Group–inflation interaction is statistically significant ($p < 0.05$).
IC-ECG = intracoronary electrocardiogram.

0.001 of group–inflation interaction for ST-segment changes) (Fig. 1).

Cardiac pain. Pain severity during balloon inflation in the 2 groups of patients is reported in Table 3. In placebo-treated patients, cardiac pain severity during the second inflation was less than that during the first inflation (57.8 ± 23.6 vs. 71.2 ± 27, $p = 0.0001$). In contrast, in gin-treated patients, cardiac pain severity during the second inflation was similar to that during the first inflation (61.4 ± 30.5 vs. 68.4 ± 27, $p = 0.14$) ($p = 0.70$ of group-inflation interaction for cardiac pain severity) (Fig. 2).

Ethanol blood levels. Ethanol blood levels, measured in the last 5 gin-treated patients, were 0 mg/dl at baseline and ranged from 16 to 34 mg/dl immediately before PCI. A strong correlation was found between the difference of ST-segment shift during the first and the second inflation and ethanol blood levels before PCI ($R = 0.90$, $p = 0.037$) (Fig. 3).

Discussion

This randomized, prospective study in humans shows that administration of a moderate dose of ethanol abolishes IPC occurring during repeated episodes of myocardial ischemia and is associated with worsening ischemia.

Our findings confirm those of previous studies showing IPC in humans during sequential balloon inflations in the setting of PCI (9,10). The limitations of the PCI model to assess IPC in humans have been critically discussed (11,12). However, the attenuation of ST-segment elevation during repeated balloon

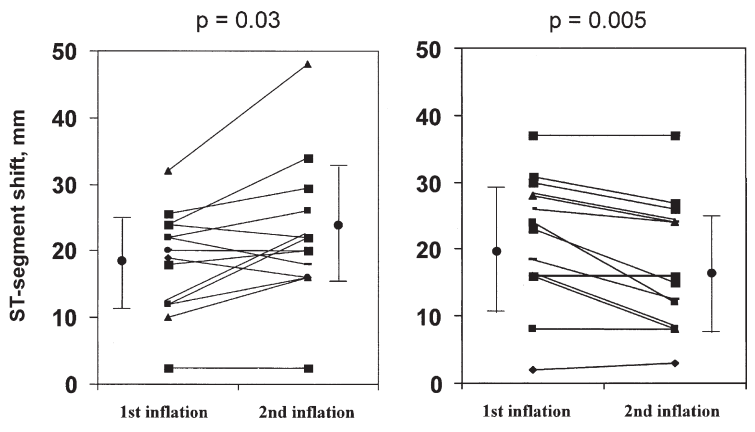

Figure 1 Plots of Individual Values of ST-Segment Shift on the IC-ECG During the First and Second Inflation in the 2 Groups of Patients

In gin-treated patients **(left)**, ST-segment changes during the second inflation were significantly greater than those during the first inflation ($p = 0.03$). Conversely, in placebo-treated patients **(right)**, ST-segment changes during the second inflation were significantly less than those during the first inflation ($p = 0.005$). IC-ECG = intracoronary electrocardiogram.

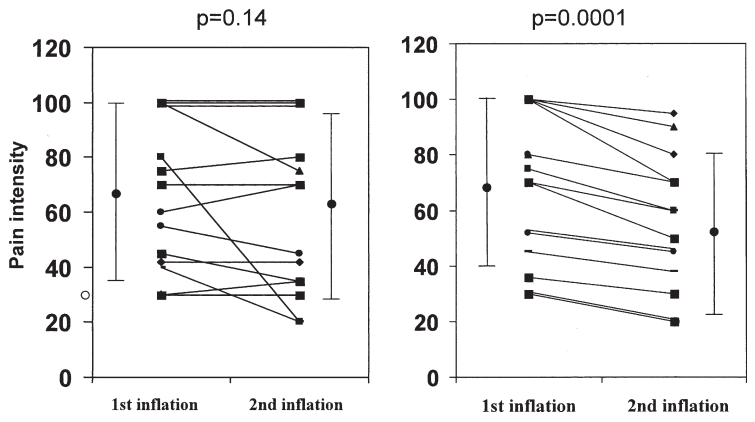

Figure 2 **Plots of Individual Values of Cardiac Pain Severity at the End of the First and Second Inflation in the 2 Groups of Patients**

In gin-treated patients **(left)**, cardiac pain severity at the end of the second inflation was similar at that at the end of the first inflation (p = 0.14). In contrast, in placebo-treated patients **(right)**, cardiac pain severity at the end of the second inflation was significantly less than that at the end of the first inflation (p = 0.0001).

inflations is concordant with changes in metabolic and echocardiographic parameters of ischemia, suggesting that ST-segment shifts are a reliable marker of the severity of ischemia (13,14). Furthermore, previous clinical studies showed that changes in coronary hemodynamics are unlikely to explain the attenuation of ST-segment shift observed during the second balloon inflation (9), which is, instead, abolished by treatments known to abolish IPC in experimental models (2).

The observation in our study that ethanol abolishes IPC in humans is in agreement with the experimental data of Krenz et al. (7), who found that in rabbits, intravenous ethanol given 10 min before ischemia prevented IPC. Of note, in the same model the effect of ethanol was time-dependent, because ethanol given 1 h before ischemia induced preconditioning-like protection resulting in a reduction of infarct size of 26% to 40%. However, in the rabbit, ethanol blood levels (28 ± 2 mg/dl) associated with this beneficial effect were similar to those associated with abolition of IPC in our human model. This discrepancy may be explained by several factors, including different doses of alcohol, different dose–effect relationships in different species, different pharmacokinetics, and different end points (12).

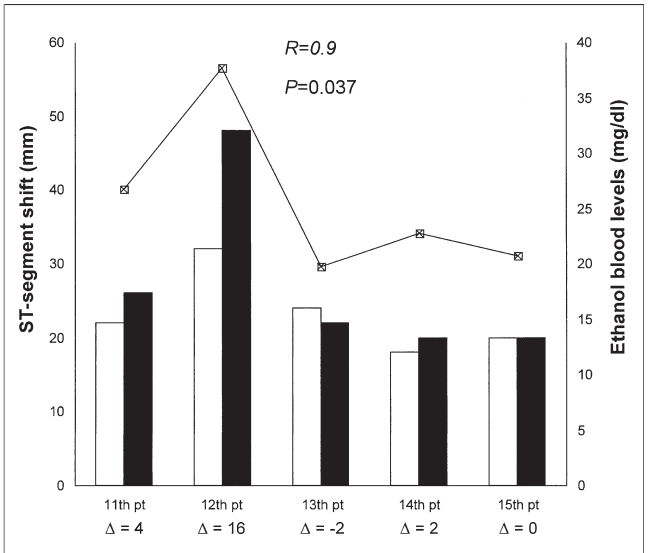

Figure 3 **Ethanol Blood Levels of the Last 5 Gin-Treated Patients Before Coronary Intervention**

In all patients, ethanol blood levels were high at the beginning of the coronary angioplasty procedure. The correlation between ethanol levels and ST-segment shift between the first and the second inflation was significant (p = 0.037). Δ = difference of ST-segment shift between second and first inflation; **solid bars** = second inflation; **open bars** = first inflation; Pt = patients.

Abolition of preconditioning is of clinical relevance. Laskey et al. (15) showed that lack of IPC according to IC or to surface ECG during PCI was associated with poor prognosis. Ishihara et al. (16) showed that a history of myocardial infarction, which potentially disrupts protective signaling of preconditioning, was associated with lack of protection by pre-infarction angina against cardiac events and mortality after acute myocardial infarction. Accordingly, abolition of IPC might help explain the higher mortality after acute myocardial infarction observed in binge drinkers as compared with those who are not binging drinkers (6) and the higher cardiovascular risk observed in heavy and binge drinkers (5).

The reason that in our study acute ethanol exposure was associated with worsening ischemia cannot be deduced by our results. Ethanol ingestion has been associated with catecholamine discharge in humans, which may increase myocardial oxygen consumption (17). However, we failed to show significant differences in heart rate and blood pressure between gin-treated and placebo-treated patients.

We cannot completely exclude that an effect of ethanol on the coronary circulation might have contributed to the negative effect on repeated balloon-induced myocardial ischemia (18–21). However, this seems unlikely because we

failed to show any effect of ethanol on baseline ST-segment level and any delay in ST-segment normalization after balloon deflation.

Another interesting finding in our study is that in placebo-treated patients, the severity of angina paralleled that of myocardial ischemia, whereas in gin-treated patients, pain severity during first and second inflation was similar in spite of worsening ischemia. The reasons for this dissociation may depend on the analgesic effects of ethanol (22).

Study limitations. Some study limitations, in addition to those inherent to the PCI model of IPC, must be considered. First, episodes of silent ischemia in the 24 h preceding the study might have occurred. However, because of the randomized nature of the study, this event should be balanced in the 2 groups. Second, we acknowledge that some differences existed between the 2 groups. However, differences were not statistically significant and were unlikely to account for the different results. Third, the electrophysiological effects of ethanol may have caused ischemic-like ST-segment shifts. However, the baseline ST-segment shift was similar in gin-treated and in placebo-treated patients. Finally, we did not assess the effects of lower doses of ethanol on IPC. Our goal, however, was to provide a possible mechanistic interpretation of the detrimental effects of binge drinking.

Conclusions

Myocardial preconditioning is a potent form of endogenous protection against ischemic injury. Thus, the demonstration in a human model that acute ethanol administration abolishes IPC is clinically relevant and suggests that intake of moderate to high doses of alcoholic beverages should be avoided in patients at risk for acute myocardial infarction.

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